What's New in Isotopes, 1950

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FOR many years the clinicians who came to me for radiologic consultation used to talk over the new advances in medical science and so keep me down to date. I always claimed that this was very nice—my friends did my reading for me. Now that I am permitted to channel my attention into the newly blossoming field of radiobiology, I am glad to undertake to do my friends' reading for them. Though the spirit is willing, yet the flesh is weak, and I find myself always behind in my reading. Moreover I am by nature intellectually excitable and readily led away on what smells like a hot trail of new development or new ideas, which may not be after all the game I am supposed to be pursuing.

I take my present assignment to be: Radioactive Isotopes in New Developments for Medicine. I shall therefore restrain myself in regard to bevatrons, linear accelerators, cosmic noise, pi and mu mesons, radioastronomy, roentgencinematography, cancer therapy by arterial injection of mustard, and the stone-in-the-anemone* method of treatment of infections and neoplastic diseases. But I might stop to mention the two new elements.

Uranium is the heaviest of the natural elements. Transuranic elements have been made by nuclear bombardment. Shall we call them "invented" rather than "discovered"? Neptunium and plutonium were made in developing the atomic bomb. By proper bombardment of these, americium and curium were made. Now two more, namely berkelium (55) and californium, have been reported. These have been made in only invisible amounts but are known by their chemical reactions. They are unstable, with half lives of 4.8 hr. and 45 min. respectively. This brings the number of known elements to 98. Prediction[64] has been ventured that elements No. 99 and 100 can exist (in their isotopes of mass 251 and 254, respectively).

The newest news in isotopes is of course the hydrogen bomb (fusion bomb), which is so new that it is not made yet[9] and maybe not possible. I will be glad to bend your ears on this subject for a couple of solid hours any time you will listen, but may not do it now. I can only express a present conviction that I do not momentarily apprehend destruction of all mankind by loosing upon the world radioactivity so enormous as to be lethal everywhere. I do think atomic warfare so bad that it ought to be given up and that statesmen ought to give first place to this problem, beside which all other problems are unimportant distractions. There is no adequate defense (except political) against even the present atom bomb, and only the most unsatisfactory therapy for radiation wounds. The Federal Government has begun general education about the A-bomb.[3]

* In Kingsley's "Water Babies," Tom, being still a bad little boy, drops stones into sea anemones to fool them into thinking a meal has come their way. Our present concept of sulfa drugs is that they imitate a related compound and take its place in cellular chemistry, but then prove misfits in the chain of essential vital reactions. Similarly the folic acid deviates for treating leukemia, and now more recently a purine deviate, guanazolo, for cancer (unhappily not successful).

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TREATMENT OF TOTAL BODY IRRADIATION

The LD 50 of x-ray or gamma ray for man is not known precisely. It lies somewhere about 400 r. From experiments on mammals one learns: Strenuous exercise increases the lethality of total body irradiation.[35] Cysteine and other innocuous sulfhydryl compounds[44] may reduce mortality by half, if given before the irradiation; NaCN likewise.[28] Bone marrow proliferating actively (after hemorrhage, for example) is less injured by irradiation than when in a quiet state.[10] This goes against the radiologists' generalization that dividing cells are more radiosensitive. The spleen is able to pinch-hit for hematopoiesis[30] after destruction of bone marrow, and spleen and appendix are able to carry on for humoral immunity reactions[29] after destruction of the lymph nodes. Should we all take to wearing gamma-ray armor over the spleen? Blood transfusions are effective in reducing irradiation death rate. But one does not see how one is to get 20 transfusions apiece for hundreds of victims after an A-bomb blast.

CATARACTS

It has long been known that irradiation of the eye can produce cataract. The dose necessary may be as small as 600 r. Lately there has been report of a couple of cases of cataract developing in scientists working with a cyclotron.[1] The supposition is that these were induced by neutron rays. A number of cataracts have developed in the Japanese A-bomb victims.[14]

BETA RAY BURNS

At the most recent A-bomb tests (Eniwetok, 1948), several scientists foolishly handled material that had just been flown through the column of smoke from the bomb. The beta irradiation on their hands was extremely high. It is noteworthy that when sufficiently intense, beta radiation is palpable. The injuries were severe.[36]

INDUSTRIAL USES OF ATOMIC POWER

Power plants using uranium instead of coal for fuel are not yet here. We are warned that even if the energy were to be had for nothing, the power would still have to be distributed, and these distribution costs are several times the cost of present fuels.[23] Atomic (nuclear power) engines will never be small enough to run an automobile. It is open knowledge that we are trying to develop nuclear energy for propulsion of aircraft (Fairchild Corp.) and of ships including submarines (General Electric Corp. and Westinghouse Corp.), but the projects themselves are secret, of course.[23]

MEDICAL AND BIOLOGICAL RESEARCH

Research in biological fields, applicable to medical problems, continues ever more actively along some of the older lines. One gets an idea by counting reports in *Nuclear Science Abstracts.* There are three or four reports per month on I^{131} for thyroid therapy, but the number of reports on its use for thyroid physiology recently has been more than double the previous six per month. Of 245 institutions getting radioactive isotopes from Oak Ridge for medical and biologic researches,[2] 167 are using I^{131}. As to P^{32} there has been no acceleration in the publication of reports—one per month on therapeutic uses, six per month on tracer uses.

P^{32} has this year been released for clinical use in treating polycythemia and leukemia. Presumably a physician may now look on it as applicable to the patient's interest. One still has to get it through an isotope committee in an institution.

It is still not demonstrated that P^{32} is superior on the whole to x-ray for management of leukemia. For polycythemia some would call it the treatment of choice. Lawrence[37] reports 172 cases, of which 121 were treated with P^{32}, with preservation of normal life expectancy.

More and more patients are being reported treated with I^{131} for Graves' disease and for thyroid cancer. One is hardly yet ready to abandon the old position, namely that the treatment of choice for hyperthyroidism is thyroidectomy.[34] One's estimate of what is best in given cases is undoubtedly going to be altered as experience perfects the clinical art of handling hyperthyroid patients with I^{131}.[60]

A number of cases of thyroid cancer with metastases are being reported held in check with I^{131} in large doses. The percentage of thyroid cancer cases amenable to such therapy remains small (about 10 per cent).[21] Some thyroid cancers that have taken up little or no I^{131} can be converted into iodine acceptors by (a) thyroidectomy[57] (probably a wise move early in the management of such a case), (b) thyrotropic hormone (30 mg. a day has been advised), (c) propylthiouracil (uptake bounces up to more than original level within a couple days of cessation of this drug),[62] (d) prolonged high-level water diuresis.[56]

NEW ATOMIC INSTRUMENTS

The instrument makers have been really busy and the apparatus available for the techniques of research with radioactive isotopes are ingenious and good. A new technique which is very promising is developed from an old one. I refer to scintillation counting, where one uses a fluorescent crystal and counts the flashes of light instead of measuring the total brightness of the glow. The first radium toy was the spinthariscope, in which alpha particles from a speck of radium produced tiny flashes of light in a zinc sulfide screen. This was the method used by Rutherford in his pioneering experiments on nuclear transmutations. Now this old technique has developed into the newest, and for some purposes promises to displace the Geiger counter. The physicists are doing new tricks with scintillation counters[33] because they are so much quicker than a Geiger counter (counting rates of a million per second), and because they are more efficient for gamma rays.

There are a number of refinements in the way of increased convenience: Machines that change samples automatically and print the measured activity of each, so that one can set one going in the evening and come back next morning to find two dozen specimens all measured; circuits to measure and record changing values of radioactivity over a period of time; circuits that calculate the counts per minute and show the value on a dial; machines to do chemical manipulations behind a lead barrier by remote control. These are nice to know about but are really pertinent only to the isotopic researcher, not to the practicing physician. The development of so-called nuclear emulsions, which have proved such a marvelous tool for the physicists in their researches on mesons, etc., in cosmic rays and from the big cyclotron, have increased the resolution of radioautographs until one can begin to see which cell in a tissue holds the radioactivity. Beta rays are least efficient at ionizing when of highest energy and produce lots of ions only after they have slowed down, which means when they are far from the source. Looking at the developed film, therefore, one cannot tell very precisely what was the point of origin. But some of the new emulsions will show tracks of beta rays even up to ¼ mev., which more than covers the energy of such biologically important tracers as carbon[11] and sulfur.

One new instrument worth mentioning is the strontium beta ray applicator for ophthalmic treatments. This is really not a new technique, for radium beta rays have been used for superficial therapy for half a century. An ophthalmic applicator using radium D has been on the market for years. The advantage of the new one is that radiostrontium (separated from fission products) is less costly, so that one may have an activity high enough to reduce the therapeutic applications to a fraction of a minute.

After waiting for more than a year, we see at last two manufacturers offering very narrow Geiger tubes designed to explore the living brain after administration of P^{32} to mark a tumor for the surgeon's guidance.[48]

Radiogallium has been shown to go rapidly to bone.[18] It is a beta emitter of fairly short half-life (14 hours). One fears to recommend any clinical trial of this for treatment of malignant tumors in the bones, because of the way radiostrontium actually produces malignant bone tumors. It seems unlikely that the difference in their half-lives will be very important if they be given in amounts to give comparable total dosage.

Radiocobalt (Co^{60}) is being made available in larger quantities and at much reduced price ($5 per curie after the first two curies). It can be produced in specific activity of several curies per gram in an old Oak Ridge pile. Newer pile design will undoubtedly make higher neutron fluxes available than the present 10^{12} n/cm^2 sec., with consequent raising of the specific activity attainable. This has induced a number of workers to draw plans for cobalt irradiators designed to use several hundred curies.[15] Such a source would be usable at much greater distance (between source and patient) than the radium "cannons" at present available. It would be more nearly comparable to a 2-million-volt x-ray tube. The lead shielding would be very heavy (half a ton or more), leading to severe engineering problems. Much weight could be saved by using a denser material than lead, such as gold or uranium. Gold is much too costly ($500 a pound, avoirdupois), and not to be rented from the Federal burial ground at Ft. Knox. Uranium has recently been released for open sale, but only 300 pounds of it, and the price quoted for the metal is $50 a pound. Dense alloys of tungsten are on the market at $10 a pound. A cobalt cannon has actually been built in England, but none as yet in this country.

Intracavitary treatment with a solution of Co^{60} inside a rubber bag has been suggested.[41] Substitution of Co^{60} for radium tubes and needles in present techniques is obviously promising.

That about ends all that is newly promising in therapy. One returns to the conviction that revolutions in medical practice may come from isotopes, but it will be through their use as research tools for making discoveries in the basic medical sciences.

TRACERS

Looking through *Nuclear Science Abstracts* one sees an increasing number of reports of tracer applications to biology—20 per month a year ago, 25 per month six months ago and 55 per month the first quarter of 1950. The variety reported is large and it is not to be expected that I can understand them all, nor that I can evaluate the importance of each and pick out for you what is most promising of the new discoveries and novel methods of attack. I shall talk about only a few, choosing those that seem scientifically curious or exciting. Another commentator might make quite different choices.

I^{131} is revealing many features of thyroid physiology: The thyroid takes up iodide, but not thyroxine.[13] In iodine starvation, I^{131} begins to enter the colloid within two minutes, but if a rat is given 22 mg. stable iodine per day the I^{131} stays in the follicle cells for an hour or more before entering the colloid. Hypophysectomy makes it stay in follicular epithelium.[38] In man, a slight increase in serum iodine increases I^{131} uptake in thyroid, but more than 5 or 10 mg. per 100 cc. inhibits it, the lower value being for clinical Graves' disease.[52] Sex hormones, male or female, depress I^{131} uptake (by pituitary depression).[42] Response of I^{131} uptake to thyrotropin can differentiate primary (thyrogenous) from secondary (pituitary) hypothyroidism.[46] Large doses of I^{131} (internal irradiation of thyroid) do not disturb thyroid function within the first ten days. But massive doses are followed by a triphasic reaction, first a release of iodide accompanied by lowering of protein-bound iodine, then a rise of protein-bound iodine (destructive action on follicles with release of colloid), and finally by myxedematous low level of serum iodine.[19] Thiocyanate is bound by thyroid more than by other tissues, but, curiously, propylthiouracil nullifies this.[63] Large doses of I^{131} in mice produce tumors (not neoplastic) of the pituitary (pituitary attempt at compensation?).[24] Epinephrine lowers I^{131} uptake in rats, but if the animals are adrenalectomized, then it increases uptake.[47] (Figure that out!) Measurement of rate of uptake by thyroid may be an improvement over per cent uptake attained, for clinical diagnosis.[43]

P^{32} continues to work hard for the biochemists interested in nucleoproteins. Synthesis of nucleic acids (ribose- and desoxyribose-) and their passage into mitochondria[32] and cytoplasm are readily followed in health, infections, regenerations and neoplasms. These experiments touch on the reproduction of chromosomes and the enzymatic activities that are the foundation of life itself. Nobody knows what revolutionary discoveries may be in the offing here. A phosphatase can transfer a phosphate group from one molecule to another and never let it become contaminated by phosphates in the surrounding solution.[5] Some enzymes have been shown to become contaminated by the substances they are working on.[31] Phosphorus turnover is 50 per cent higher in gastric carcinomas than in adjacent normal mucosa.[25] Will someone turn this to account for clinical diagnosis? By measuring mitotic activity of testicular epithelium, it has been shown that hypophyseal stimulation of testis is inhibited by the pineal.[54] Mosquitoes have been successfully labeled with P^{32} as an aid to control studies.[27]

Carbon 14 is a tracer whose usefulness is as wide as organic chemistry. One firm* offers 59 organic compounds labeled with radiocarbon (@ $100 to $500 a milligram). There is a little C^{14} in the atmosphere due to action of cosmic rays on nitrogen. Old stores of carbon show lesser activities, of course, because the C^{14} decays away (half gone in 5,000 years).[4] This has permitted measurement of the age of Egyptian mummies and confirmation of historical chronology. Some other C^{14} researches are interesting and perhaps important: Fat given by vein is readily metabolized.[22] Arterial wall is able to synthesize fatty acids from acetate.[12] (Has this any meaning for atheroma?) Normal persons break down one-half to three-quarters of dietary fat in the first 24 hours, but this is greatly lessened in hyperlipemic patients.[53] (This was determined with I^{131} as a tracer.) Only a little radiocarbon is retained in the body, but its location and concentration are

* Tracerlab: California office is at 2295 San Pablo Avenue, Berkeley 2, California.

uncertain; therefore it is still considered hazardous for human experimentation.[50]

Hemoglobin has been studied with C^{14} as well as Fe^{55} and Fe^{59}. Carboxyl-labeled glycine enters the globin, but not the porphyrin.[26] The globin remains chemically quite static. Iron turnover in plasma is astonishingly rapid. Iron utilization is high in iron depletion states and depressed in hemochromatosis, etc.[20] Some hemoglobin can be formed in circulating blood. Nucleated red cells (ducks) take up iron[49] and so do normoblasts and reticulocytes[59] (mammals), but normal adult mammalian red cells do not. Life of red cells in man is about 115 days.[6] In sickle-cell anemia, however, they do not live out their normal life, but are indiscriminately destroyed, some soon, some late.[39]

Penicillin has been successfully labeled with S^{35} and shown to enter the cytoplasm of susceptible staphylococci, not just bound to the cell wall.[17] What this means for ultimate understanding of the action of antibiotics I don't yet know.

Zinc is all through the body in very small amount. There seems to be some mechanism for its conservation and re-utilization. The concentration in human leukocytes is 25 times as high as in the erythrocytes.[58] In leukemia the amount per cell falls off but comes up again in a remission.

Gold is found to concentrate in arthritic joints and also in the wall of an abscess.[8] Silver also concentrates in abscesses.[61] Whether this can be used to diagnose deep-seated abscess we do not yet know.

Na^{24} has been used for some time to test the state of peripheral circulation, by giving a dose intravenously and measuring its appearance and persistence in a limb. More recently it has been given locally (into the muscle) and its rate of disappearance measured.[16] The diagnosis of cardiac disturbances by studying the curve of activity as a dose of Na^{24} moves through the heart has apparently made little further progress in the past year.[45]

Radiomercury has been used to study action of mercurial diuretics. There is an interesting first brief phase of low urine output with high concentration of mercury.[40]

Stable isotopes have been used in fewer researches. They are more difficult to measure. Moreover the radioactive ones are capable of revealing themselves in enormously greater dilution. Heavy hydrogen is of course the most readily and widely useful. Heavy water (D_2O) is the ultimate standard method of estimating total body water. It has been shown by comparison that the antipyrene method is clinically satisfactory.[51] Heavy nitrogen was used to label uric acid, and with this the body pool of uric acid was determined to be fifteen times as large in gout as in health.[7]

The foregoing listing holds some five dozen items that seemed to me novel, important or scientifically stimulating. Obviously there is not time for exploration of the implications of even a fraction of them. If some of you pick up one or two items that fit into the kaleidoscope of your cogitations and make a pattern, I shall feel this long recital has not been boredom unrelieved.

I have one more curious item. By irradiation with twenty million volt x-rays (200 r), living rats have been rendered perceptibly radioactive with a half-life of two minutes.

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